REMARKS

In the Office Action dated June 13, 2005, claims 25-42 are pending and under examination. Claims 25-42 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enabling support. Claims 25-42 are also rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 29, 35 and 41 are rejected under 35 U.S.C. §102(b) for allegedly encompassing consumption of commonly known popular beverages that contain certain amounts of sodium citrate. The application is objected to for certain informalities in the drawings and drawing description.

This Response addresses each of the Examiner's objections and rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The application is objected to for certain informalities in the drawings and drawing description. Applicants have amended the specification to properly reference the drawing numbers. Applicants are also providing substitute drawings for Figures 7A-7B and Figures 9A-9B, which are now properly labeled. As such, the objection to the application based on the informalities in the drawings and drawing description is obviated. Withdrawal of the objection is therefore respectfully requested.

Claims 29, 35 and 41 are rejected under 35 U.S.C. §102(b). The Examiner contends that the methods of these claims read on consumption of commonly known popular beverages, such as ice-tea and soda, which contain certain amounts of sodium citrate.

Applicants respectfully submit that the claimed methods are directed to treatment of Alzheimer's patients and include the step of administration of a therapeutically effective amount

of a zinc-binding agent to an Alzheimer's patient. Consumption of popular beverages by the general public by no means constitutes a therapeutic treatment directed specifically to Alzheimer's patients. Furthermore, Applicants have canceled claims 29, 35 and 41 in favor of the newly presented claims. Therefore, the rejection of claims 29, 35 and 41 under 35 U.S.C. §102(b) is moot. Withdrawal of the rejection is therefore respectfully requested.

Claims 25-42 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

More specifically, claim 37 is objected to because of the recitation "an effective amount". The Examiner contends that the claim does not state an objective, and therefore it is not clear what the amount is effective for.

Applicants respectfully submit that claim 37 is not ambiguous. It is clear from the language of claim 37 that the amount of agent is effective for modulating the interaction within the central nervous system between a divalent or trivalent cation and/or heparin with amyloid precursor protein (APP) of the patient, thereby reducing aberrant protease-mediated processing of amyloid precursor protein (APP).

Claim 37 is also objected to for the recitation "incorrect ... processing".

Applicants have amended claim 37 to recite "abnormal ... processing". Support for this amendment is found in the specification, e.g., page 1, lines 21-26; page 23, line 15, for example. Based on the instant disclosure, those skilled in the art would clearly understand the meaning of "abnormal ... processing" without ambiguity.

Applicants further respectfully submit that other grounds of the Examiner's rejection under 35 U.S.C. §112, second paragraph, have been addressed by the foregoing amendments to

the claims. Accordingly, it is respectfully submitted that the claims, as presently recited, are not indefinite. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is therefore respectfully requested.

Claims 25-42 are also rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enabling support.

With respect to claims 25-26, 31-32 and 37-38, the Examiner contends that these claims are single means claims which, by broadest reasonable interpretation, encompass the use of any known factor, including lethal drugs. The Examiner states that this type of claim (single means) have been held to be non-enabling for the scope of the claim in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) because the specification disclosed at most only those means known to the inventor.

Applicants respectfully disagree with the Examiner and do not believe that *In re Hyatt* is particularly applicable to the present circumstances. However, in an effort to advance prosecution of the present application, Applicants have amended the claims to further define the agent as a zinc-binding agent which modulates the interaction between a divalent or trivalent cation and/or heparin with APP.

With respect to claims 27-30, 33-36 and 39-42, which specifically recite zinc-binding agents, the Examiner contends that the instant specification fails to provide sufficient guidance to one skilled in the art on how to practice the instant methods.

In the first instance, the Examiner states that at the time the present invention was made, the art recognized that NFT and Aβ plaques constituted two major brain abnormalities in Alzheimer's disease (AD) pathology. However, the Examiner contends that it was not

recognized in the art that zinc plays a critical role in the etiology of Alzheimer's disease.

Applicants respectfully submit that it is indeed a unique recognition of the present invention that by modulating the levels of divalent cations (particularly zinc) or heparin, the range, type and/or extent of APP cleavage can be altered such that aberrant protease-mediated processing of APP can be reduced or inhibited. See page 7, lines 1-7 of the present specification. Thus, the deficiency of the prior art relating to the role of zinc does not warrant a conclusion of non-enablement, as the present application provides adequate teaching in this regard.

Furthermore, the Examiner states that the sole working examples in the specification pertain to *in vitro* binding experiments. The Examiner acknowledges that it is not necessary that Applicant understood or disclosed the mechanism by which the invention functions. However, the Examiner contends that in this case, in the absence of such an understanding, no extrapolation can be made from the results of limited *in vitro* protein binding studies to the claimed method of treatment of Alzheimer's disease. Moreover, the Examiner alleges that the specification provides no factual evidence or sound scientific reasoning to support a conclusion that administration of zinc-binding agents could be effective to treat Alzheimer's disease.

In response, Applicants provide herewith a Declaration of Dr. Roberto Cappai in support of the enablement of the claimed methods.[1] Applicants first direct the Examiner's attention to Paragraph 5 of the Declaration, where Dr. Cappai discussed the prior art background with respect to APP accumulation and processing in relation to Alzheimers' disease. Further, in Paragraph 6 of the Declaration, Dr. Cappai discussed the recognition in the '924 application that zinc-binding agents modulate APP processing and are therefore beneficial for the treatment of

1. Applicants will submit the executed declaration as soon as it is received by counsel.

Alzheimer's disease. Dr. Cappai then concluded that it is his scientific opinion that the '924 application has provided to those skilled in the art sound scientific reasoning relating to the basis of the claimed methods. See Paragraph 7 of the Declaration.

Dr. Cappai further testified that it is his scientific opinion that, based on the teaching in the '924 application and the information available prior to the filing of the '924 application, those skilled in the art would be able to practice the methods claimed in the '924 application. See Paragraph 8 of the Declaration. As further explained in Paragraphs 9-11 of the Declaration, at the time the '924 application was filed, chelators of cations, particularly zinc chelators, were well-known to those skilled in the art; and additionally, those skilled in the art could readily determine whether a chelator is capable of crossing the blood brain barrier (BBB).

Consistent with the proposition in the '924 application that a zinc-binding agent capable of crossing the BBB would effectively modulate APP processing, Dr. Cappai presented data showing that a specific zinc chelator disclosed in the '924 application, CP94, alters APP processing, resulting in the reduction of Aβ40 levels in an *in vitro* system. See Paragraph 12 of the Declaration. In addition, several other zinc-binding agents, including clioquinol (CQ), also altered APP processing resulting in the reduction of Aβ40 levels *in vitro*. See Paragraph 13 of the Declaration.

Moreover, Dr. Cappai presented evidence showing that the zinc-binding agent, clioquinol (CQ), which has shown to be effective in reducing Aβ40 levels *in vitro*, was also effective in reducing toxic Aβ levels *in vivo* and inhibited cognitive decline in human patients.

Applicants acknowledge that additional experimentation may be necessary in order to practice the present invention, e.g., optimization of dosages of a zinc-binding agent. However,

some experimentation is permissible. *See, In re Wands*, 858 F.2d. 731, 736-737, 8 U.S.P.Q. 1400, 1404 (Fed. Cir. 1988). Necessary experimentation is not determinative of the question of enablement; only undue experimentation is fatal under the provisions of 35 U.S.C. § 112, first paragraph. Based on the teachings of the instant disclosure, such experimentation is within the scope of one skilled in the art and is not undue. Such contention is supported by Dr. Cappai's Declaration, which demonstrates that based on the present teaching, those skilled in the art are able to practice the presently claimed methods in the absence of undue experimentation.

In view of the foregoing, it is respectfully submitted that the enablement rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

It is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser
400 Garden City Plaza-STE 300
Garden City, New York 11530
(516) 742-4343
XZ:ab

Encls.: Replacement Sheets and
Annotated Sheets Showing Changes (Figs. 7A-7B and 9A-9B)
Declaration of Dr. Cappai (with Exhibits A-L attached thereto)

AMENDMENTS TO THE DRAWINGS:

The attached sheets of drawing include changes to Figures 7(a)-7(b) and Figures 9(a)-9(b).

Replacement sheets for Figures 7A-7B and Figures 9A-9B are attached hereto.

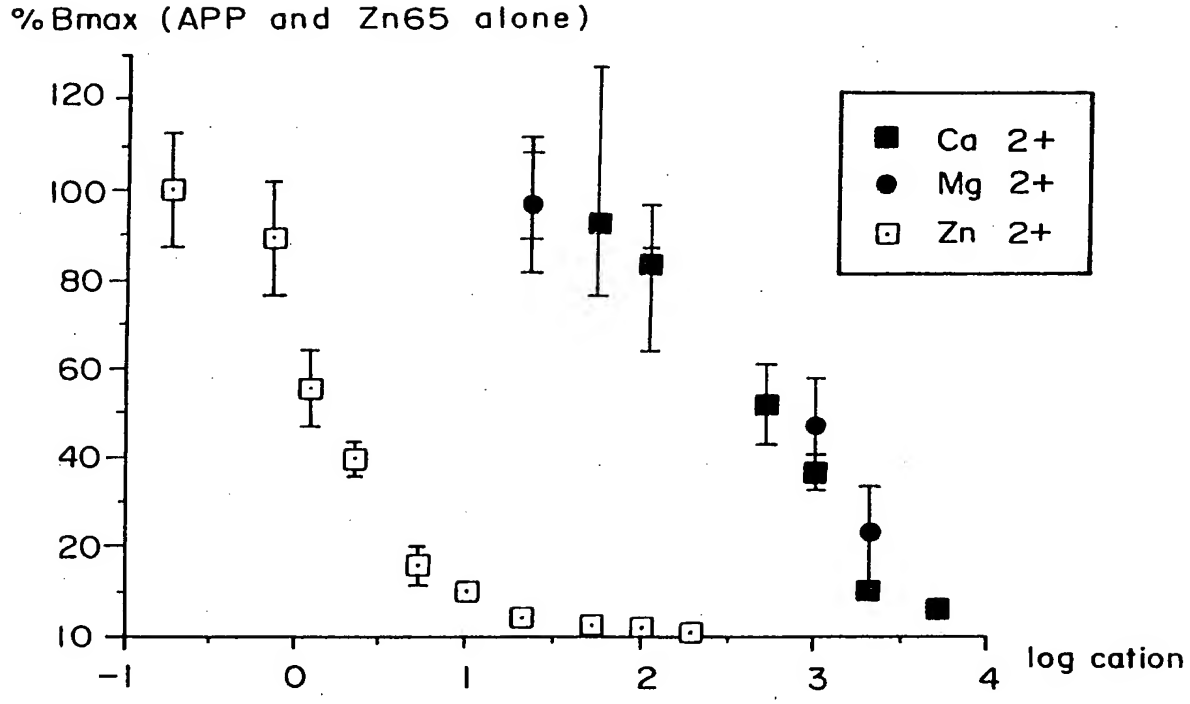


FIG. 7~~(a)~~ A

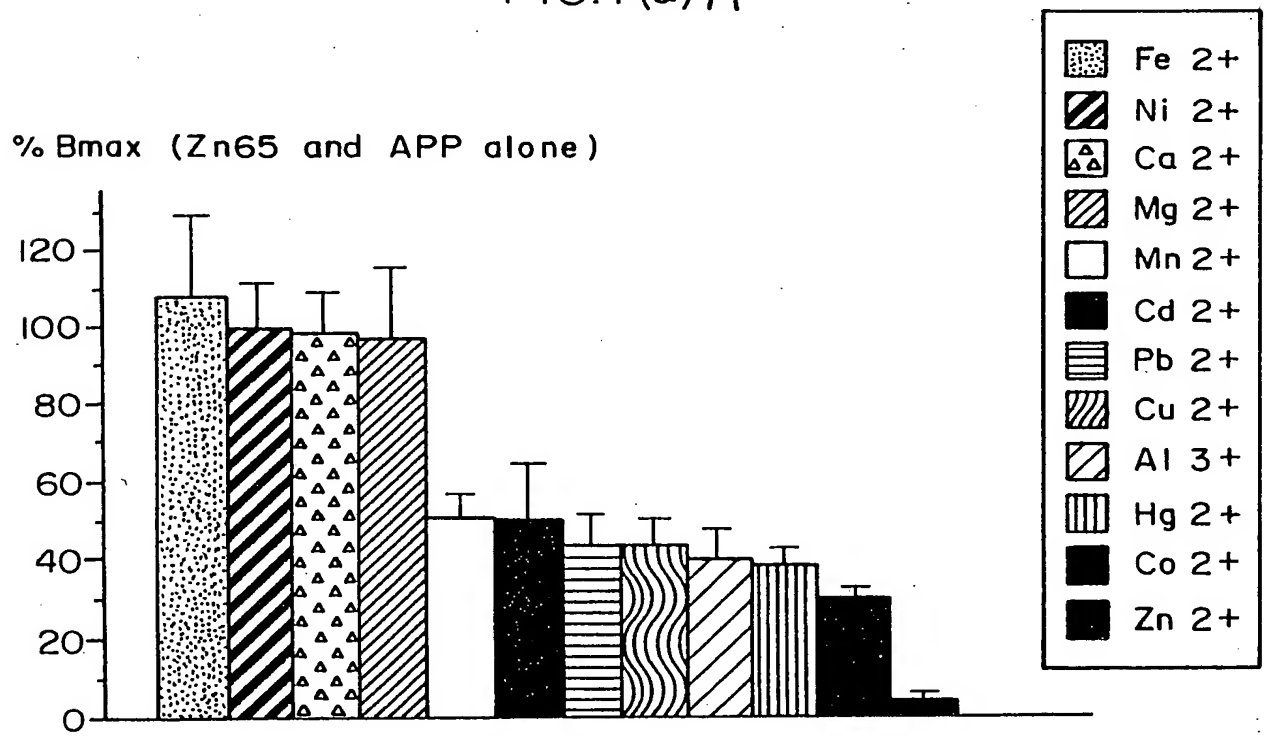
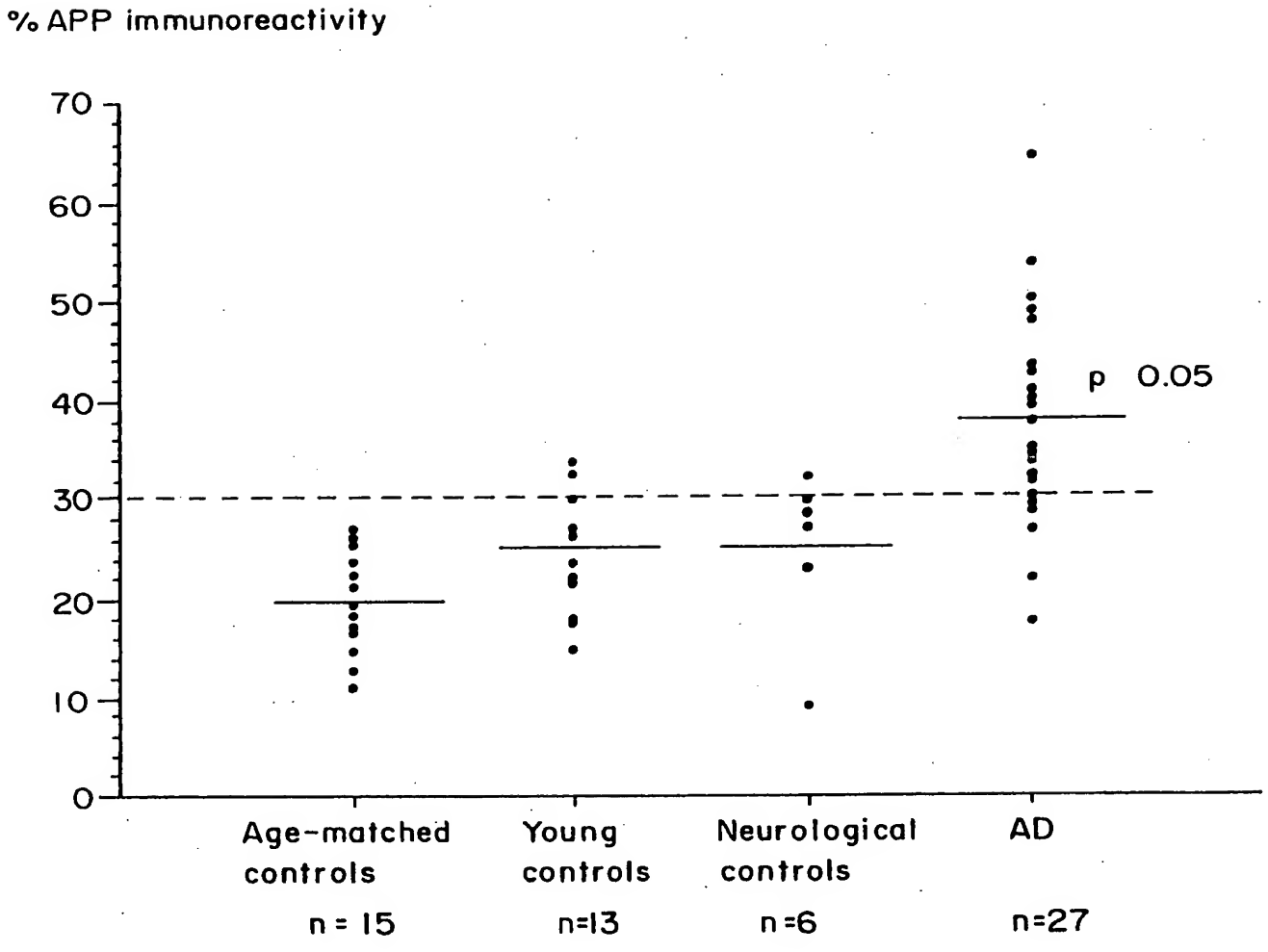


FIG. 7~~(b)~~ B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50
40
30
20
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p 0.05
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Young controls
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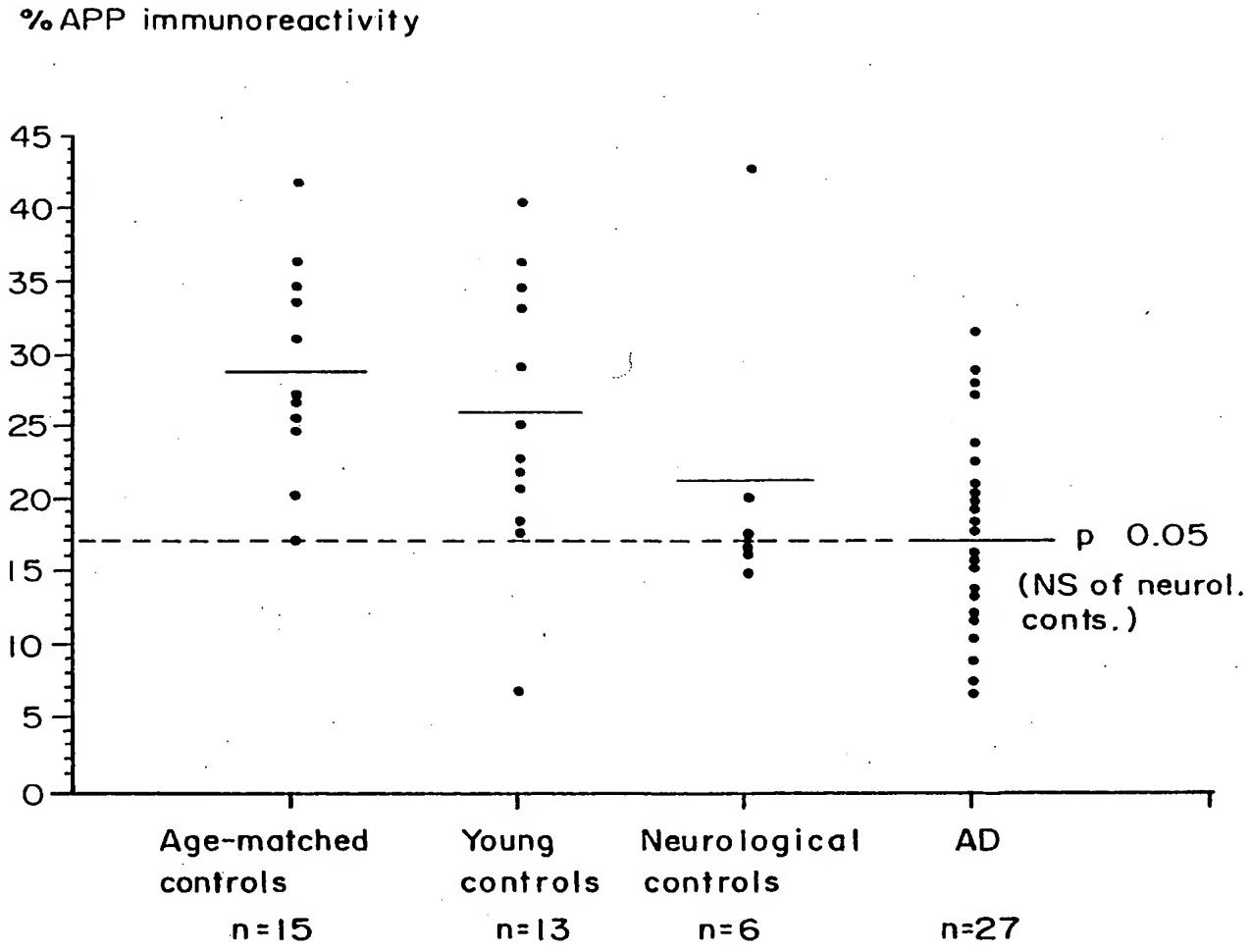
Neurological controls
n=6
AD
n=27

FIG. 9~~(a)~~ A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40
35
30
25
20
15
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5
0
p 0.05
(NS of neurol. conts.)
Age-matched controls
n=15
Young controls
n=13
Neurological controls
n=6
AD
n=27

FIG. 9~~(b)~~ B